IRGANOX 1010

Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane

CAS No. 6683-19-8

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CONTENTS

1. MELTING POINT

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8
Method:	Estimated by the MPBPWIN Program (v. 1.40),[1] using the adapted Joback method and the Gold and Ogle method.
GLP:	No
Year:	2000
Results:	349.8 °C
Remarks:	The melting point calculation by an accepted method is assigned a reliability code of 2f.[2]
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998 [2]See general reference, p. 34.

2. BOILING POINT

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8
Method:	Estimated by the MPBPWIN Program (v. 1.40)[1] using the adapted Stein and Brown method.
GLP:	No
Year:	2000
Results:	1130.4 °C
Remarks:	The boiling point calculation by an accepted method is assigned a reliability code of 2f.
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

3. VAPOR PRESSURE

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8
Method:	Estimated by the MPBPWIN Program (v. 1.40),[1] using the modified Grain method.
GLP:	No
Year:	2000
Results:	1.2×10^{-33} mm Hg
Remarks:	The vapor pressure calculation by an accepted method is assigned a reliability code of 2f.
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

4. PARTITION COEFFICIENT

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8
Method:	Directive 84/449/EEC, A.8 "Partition coefficient", 1985
Temperature:	25°C
GLP:	Yes
Year:	1985
Results:	Log Pow = 23
Remarks:	The partition coefficient was calculated using the computer program CLOGP.3. Results are consistent with a partition coefficient value of 19.6 estimated by KOWWIN (v. 1.66).[1] This study is assigned a reliability code of 1 (reliable without restriction) as it was conducted under relevant guidelines.
References:	"Report on Partition Coefficient", Ciba Geigy Ltd., Basel, Switzerland. Dr. P. Moser, 06/14/85. [1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

5. WATER SOLUBILITY

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8
Method:	Directive 84/449/EEC, A.6, "Water Solubility", 1989
Temperature:	20 °C
GLP:	No
Year:	1985
Results:	$< 10^{-4}$ g/L Of very low solubility or not soluble
Remarks:	Results are consistent with a calculated value of 1.4×10^{-18} using the WSKOW Program (v. 1.37).[1] This study is assigned a reliability code of 2 (reliable with restrictions) as it was not conducted under GLP guidelines.
References:	"Report on water solubility, Irganox 1010," Ciba-Geigy Limited, Basel, Switzerland, 1985 [1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

6. PHOTODEGRADATION

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8
Method:	Estimated by the AOP program (v. 1.90),[1] which estimates rate constants and half-lives of atmospheric reactions of organic compounds with hydroxyl radicals and ozone in the atmosphere.
GLP:	No
Year:	2000
Results:	For reaction with hydroxyl radicals, the predicted half-life of the chemical is rapid. Rate constant: 106.3×10^{-12} cm^3/molecule-sec Half-life: 1.2 h
Remarks:	The photodegradation calculation by an accepted method is assigned a reliability code of 2f.
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

7. STABILITY IN WATER

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8
Method:	Estimated by the HYDROWIN Program (v. 1.67).[1]
GLP:	No
Year:	2000
Results:	At 25 °C $t_{1/2}$ (pH 8) = 75.4 days $t_{1/2}$ (pH 7) = 2.1 years
Remarks:	The stability in water calculation by an accepted method is assigned a reliability code of 2f.
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

8. THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8
Method:	Estimated by Level III Fugacity Model.[1]
Year:	2000
GLP:	No
Results:	Distribution using level III fugacity model

Air	0.00195%
Water	1.06%
Soil	43.2%
Sediment	55.7%

Remarks:	The fugacity calculation by an accepted method is assigned a reliability code of 2f.
References:	[1]Syracuse Research Corporation, Syracuse, NY

9. BIODEGRADATION

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8 Batch No. EN 97149.44
Method:	OECD Guideline 301 B "Inherent Biodegradability: Modified Sturm Test" (Paris, 1981). Bacteria was collected from a sewage treatment plant. The only deviation from the guideline related to the volume of the test solution which was reduced from 3.0 to 1.5 L. Biodegradation was calculated on the basis of the theoretical carbon content of the test substance and the cumulative quantities of carbon dioxide determined on the days of measurement.
Test Type:	Aerobic
Inoculum:	Fresh sewage treatment plant sample (per guideline)
Concentration of the chemical:	10 mg/L and 20 mg/L for the test substance 20 mg/L reference chemical (aniline)
Medium:	Sewage sludge (per guideline)
GLP:	Yes
Year:	1985
Results:	Degradation: 10 mg/L: 5 % after 28 days 20 mg/L: 4 % after 28 days Under the test conditions, no biodegradation was observed.
Conclusion:	Substance is not biodegradable according to OECD definition.
Remarks:	This study is considered reliable (reliability code 1). The study was conducted under OECD and GLP Guidelines.
Reference:	"Report on the Test for Ready Biodegradability of TK 10042 in the Modified Sturm Test", Ciba Geigy, Basel, Switzerland. Dr. A. de Morsier, 04/11/85.

10. ACUTE TOXICITY TO FISH

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8 Batch No. EN 97149.44
Method:	OECD Guideline No. 203 (Paris 1981). This study was performed as a limit test with a concentration of 100 mg/L (nominal). The highest vehicle concentration used was 954 mg/L.
Type of test:	Static
Species:	Zebra Fish (Brachydanio rerio)
Supplier:	West-Aquarium, D-3422 Bad Lauterberg
Length:	25 mm (20-28 mm)
Weight:	0.13 g (0.09-0.18 g)
Loading:	0.1 g/L
Exposure period:	96 h
Analytical monitoring:	Yes
GLP:	Yes
Year:	1985
Results:	LC_{50} (24 h) = > 100 mg/L LC_{50} (48 h) = > 100 mg/L LC_{50} (72 h) = > 100 mg/L LC_{50} (96 h) = > 100 mg/L NOEC = 100 mg/L
Remarks:	This study is assigned a reliability code of 1 (reliable without restrictions) according the criteria established by Klimisch *et al* (1997), as it was conducted under OECD and GLP Guidelines.
Reference:	"Report on the test for acute toxicity of TK 10042 to Zebra Fish", Ciba Geigy, Limited, Basel, Switzerland. Dr. A. de Morsier, 04/01/85.

11. TOXICITY TO AQUATIC PLANTS

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8 Batch No. EN 146553.4; purity: 99%
Method:	87/302/EEC pp 89-94 Algal Inhibition Test Closed-system. No deviations from the above stated guideline occurred during the conduct of this study. The EC values were calculated according to Berkson, JASA 48 (1953), 569-599.
Species:	Green Algae (Scenedesmus subspicatus)
Endpoint:	Growth rate
Exposure period:	72 h
Initial Cell Density:	10^4 cells/mL
Test Concentrations:	1.23, 3.7, 11, 33 and 100 mg/L (nominal)
Vehicle:	Alkylphenol-polyglycolether
Analytical monitoring:	Yes
GLP:	Yes
Year:	1992
Results:	EC_{50} (0 – 72 h) = > 100 mg/L $NOEC_b$ (0 – 72 h) = 100 mg/L
Remarks:	This study is assigned a reliability code of 1 (reliable without restrictions) according the criteria established by Klimisch *et al* (1997).
Reference:	"Report on the Growth Inhibition Test of Irganox 1010 to Green Algae (Scenedesmus subspicatus)", Ciba-Geigy, Limited, Basel, Switzerland. Dr. A. von Schulthess, 11/12/92.

12. ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8 Batch No. 97149.44
Method:	OECD Guideline No. 202 (Paris 1981). A deviation from the OECD Guideline was the vehicle concentration (highest was 954 mg/L). The nominal concentrations of the test compound were 10, 18, 32, 58 and 100 mg/L. The organisms used in this study were 0 – 22 h old and were unfed. EC values were graphically determined.
Type of test:	Static
Species:	Daphnia Magna Straus 1820
Exposure period:	24 hours
Analytical monitoring:	Yes
GLP:	No
Year:	1985
Results:	EC_{50} (24 h) = > 86 mg/L EC_0 (24 h) = 31 mg/L EC_{100} (24 h) = > 86 mg/L
Remarks:	This study is assigned a reliability code of 2a (reliable without restrictions) according to the criteria established by Klimisch *et al* (1997). This study was conducted under OECD, but not GLP guidelines.
Reference:	"Report on the Test for Acute Toxicity of TK 10042 to Daphnia Magna", Ciba-Geigy Limited, Basel, Switzerland. Dr. A. de Morsier, 03/29/85.

13. ACUTE TOXICITY

Several studies were conducted to assess the acute toxicity. Although all studies are listed, the oral study is selected for evaluation of this endpoint.

ORAL

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8 Batch Nos. MA-11 and MA-12
Method:	Two batches of the test material (MA11 and MA12) were tested at each dose level. Animals were observed for clinical signs of toxicity and mortality daily for 14 days. Initial and final body weights were recorded. Necropsy was performed at the end of the observation period. No animals died during the study.
Species/strain:	Sprague Dawley Rats
Sex:	Males and Females
No. Animals/Group:	2/sex
Doses:	4556, 6834 or 10250 mg/kg bw
Vehicle:	25% (w/v) suspension in corn oil
Post dosing observation period:	14 days
GLP:	No
Year:	1968 - 1974
Results:	LD_{50} > 10,250 mg/kg bw No clinical signs of toxicity were observed. Irganox 1010 is considered acutely nontoxic by the oral route of administration
Remarks:	This study is assigned a reliability code of 2 (reliable with restrictions) based on the criteria described by Klimisch *et al* (1997). This study was not conducted under GLP or OECD guidelines. However, these findings validate several earlier studies conducted in rats which found the LD_{50} to be greater than 10,000 mg/kg. The doses in these studies ranged from 2,500 to 10,250 mg/kg bw.

Reference:	"Acute Oral Toxicity Studies with Two Samples in Albino Rats", IBT No. 601-04522. Industrial Bio-Test Labs, Inc., M.L. Keplinger, 02/15/74 .
Additional References:	"Acute Oral Toxicity Study in Albino Rats", IBT Report No. A2060, Industrial Bio-Test Labs, Inc. M.L. Keplinger, 09/19/72.
	"Acute Oral Administration (LD50) in Male Rats", Geigy Pharmaceuticals, Dept. of Toxicology, Technical Report. 02/23/68.
	"Acute Oral Administration (LD50) in Female Rats", Geigy Pharmaceuticals, Dept. of Toxicology, Technical Report. 02/23/68.

INHALATION

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8
Method:	Rats were placed in a nose-only exposure system, and exposed to an aerosol of the test compound. During the exposure, concentration and particle size were monitored. Animals were observed during exposure at 1, 2, and 4 hours as well as 2 hours post-exposure and daily for 14 days.
Type:	LC_{50}
Species/strain:	Rat
No. animals/group:	10 Males/10 Females/group
Doses:	0, 762, and 1951 mg/m^3
Exposure time:	4 hours
Post exposure observation period:	14 days
GLP:	No
Year:	1980
Results:	$LC_{50} > 1951$ mg/m^3
Remarks:	This study is assigned a reliability code of 2e. This study was not conducted under GLP or OECD guidelines, but does meet generally accepted scientific standards, is well documented, and is acceptable for assessment.
Reference:	"Acute aerosol inhalation toxicity in the rat of TK-10042," Ciba-Geigy Limited, Experimental Toxicology, Project 801603, 1980.

DERMAL

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8
Method:	The test material was applied to albino rabbits (4/group) at a dose of 100, 316, 1000, or 3160 mg/kg body weight. The material was applied to the closely-clipped abdominal skin for 24 hours, and animals were observed for an additional 14 days.
Type:	LD_{50}
Species/strain:	Rabbit
Doses:	100 mg/kg 316 mg/kg 1000 mg/kg 3160 mg/kg
Exposure period:	24 hours
Post exposure observation period:	14 days
GLP:	No
Year:	1964
Results:	> 3160 mg/kg bw
Remarks:	This study is assigned a reliability code of 2e. This study was not conducted under GLP or OECD guidelines, but does meet generally accepted scientific standards, is well documented, and is acceptable for assessment.
Reference:	"Acute Dermal Application - Albino Rabbits," Ciba-Geigy Limited, Basel, Switzerland, 5/19/64.

14. GENETIC TOXICITY IN VIVO

Several *in vivo* genetic toxicity studies were conducted.

A

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8 Batch No. EN 28303
Method:	This study was not conducted under OECD guidelines. Male mice (20/group) were administered a single gavage dose of 0, 1000 or 3000 mg/kg in aqueous carboxymethylcellulose (0.2 mL/kg bw). Males were mated with females for up to 6 weekly mating periods. Pregnant females were necropsied on Day 14 of pregnancy.
Type:	Dominant lethal assay
Species/strain:	Albino mice (NMRI derived)
Sex:	Male
Route of Administration:	Gavage
Exposure period:	Single exposure
Doses:	1000 and 3000 mg/kg
GLP:	No
Year:	1975
Results:	No evidence of dominant lethal effects was noted. There were no differences in mating ratio, number of implantations or embryonic deaths between controls and treated.
Remarks:	This study is assigned a reliability code of 2e (meets generally accepted scientific standards, is well documented, and acceptable for assessment).
Reference:	"Dominant Lethal Study on TK 10042, Mouse (Test for Cytotoxic or Mutagenic Effects on Male Germinal Cells), Experiment No. 327539. Ciba Geigy, Limited, Basel, Switzerland. Dr. H. Fritz, 09/12/75.

B

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8 Batch No. EN 1343
Method:	This study was not conducted under OECD or GLP guidelines. Animals (6/group) were gavaged with either 500, 1000 or 2000 mg/kg test material in 0.5% carboxymethylcellulose (CMC) (20 mL/kg). Positive controls animals were administered 128 mg/kg cyclophosphamide in 0.5% CMC (20 mL/kg) and negative controls were administered 20 mL/kg 0.5% CMC. Treatment consisted of daily administration on 2 consecutive days. Twenty-four hours after the second application the animals were sacrificed and bone marrow was harvested from the shaft of both femurs. Bone marrow cells were scored for chromosomal anomalies.
Type:	Somatic mutation assay
Species/strain:	Chinese hamster
Sex:	Male/Female
Route of Administration:	Gavage
Exposure period:	2 Days
Doses:	500, 1000 and 2000 mg/kg
GLP:	No
Year:	1977
Results:	In all groups, the percentage of cells displaying anomalies of nuclei did not differ significantly from the negative control. The test material is considered to be nonmutagenic.
Remarks:	This study is assigned a reliability code of 2e (meets generally accepted scientific standards, is well documented, and acceptable for assessment).
Reference:	"Nucleus Anomaly Test on Somatic Interphase Nuclei, TK 10042, Chinese Hamster (Test for Mutagenic Effects on Bone Marrow Cells)", Ciba Geigy, Limited, Basel-Switzerland. Dr. D. Muller, 10/26/77.

C

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8 Batch No. EN 1343
Method:	This study was not conducted under OECD guidelines. Animals (4/sex/dose group) were gavaged once daily for 2 consecutive days with either 0, 500, 1000 or 2000 mg/kg bw test material in 2% aqueous solution of sodium carboxymethylcellulose (CMC) (20 mL/kg). Positive controls were administered 64 mg/kg cyclophosphamide in 2% CMC (20 mL/kg). The animals were injected with 10 mg/kg colcemide 2 hours after administration of the second dose and sacrificed 4 hours later. Bone marrow was harvested and analyzed for chromosomal aberrations (100 metaphases/animal).
Type:	Somatic mutation assay
Species/strain:	Chinese Hamsters (Cricetulus griseus), male and female
Route of Administration:	Gavage
Exposure period:	2 Days
Doses:	500, 1000 and 2000 mg/kg
GLP:	No
Year:	1978
Results:	The chromosome displays from the negative control group and the intermediate and high dose groups showed no aberrations. In the animals of the low dose group, one metaphase per 400 cells with chromatid-type aberration in the form of a break was detected. This incidence is within the frequency observed in historical controls and is therefore considered to be spontaneous in origin. The test material is considered to be nonmutagenic.
Remarks:	This study is assigned a reliability code of 2e (meets generally accepted scientific standards, is well documented, and acceptable for assessment).
Reference:	"Chromosome Studies in Somatic Cells, TK 10042, Chinese Hamster Test for Mutagenic Effects on Bone Marrow Cells." Experiment No. 764028. Ciba Geigy, Limited, Basel, Switzerland. Dr. D. Muller, 09/27/78.

15. GENETIC TOXICITY IN VITRO

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8
Method:	This study was not conducted under OECD guidelines, but was conducted using the methods described by Ames *et al* (1973, 1975). The material was tested for mutagenic effects on histidine auxotrophic mutants of Salmonella typhimurium. Cultures were prepared from frozen stock, and on the following day the standard plate test was carried out. The concentrations of the test substance used without microsomal activation were: 10, 25, 50, 100 and 250 µg/0.1 mL; concentrations with microsomal activation were: 5, 10, 25, 50 and 100 µ g/0.1 mL. In the experiments in which the substance was metabolically activated, 0.5 mL of the activation mixture (S9 fraction of liver from rats induced with Aroclor 1254 plus co-factors) was added. Positive controls in the form of spot tests were also included.
Type:	Reverse mutation assay
System of testing:	S. typhimurium TA 98, TA 100, TA 1535, TA 1537
Concentration:	10-250 µg/0.1 mL
Metabolic activation:	With and without S9 fraction of liver from rats induced with Aroclor 1254 plus co-factors
GLP:	No
Year:	1977
Results	No increase in reverse mutations with or without metabolic activation. Cytotoxicity conc: Not reported. Precipitation conc: 100 µg/0.1 mL
Remarks:	This study is considered scientifically sound and follows methods decribed by Ames *et al.* (1973 & 1975). The study is assigned a reliability code of 2e (meets generally accepted scientific standards, is well documented, and acceptable for assessment).
References:	"Salmonella/Mammalian Microsome Mutagenicity Test with TKA 10042 (Test for Mutagenic Properties in Bacteria." Ciba Geigy, Limited, Basel, Switzerland. Dr. P. Arni, 04/20/77.

Ames, B.N., Lee, F.D., and Durston, W.E., "An improved bacterial test system for the detection and classification of mutagens and carcinogens, Proc. Natl. Acad. Sci. USA, 70, 782-786, 1973.

Ames, B.N., Durston, W.E., Yamasaki, E., and Lee, F.D., "Carcinogens are mutagens: a simple test system combining liver homogenates for activation and bacteria for detection," Proc. Natl. Acad. Sci. USA, 70, 2281-2285, 1973.

Ames, B.N., McCann, J., and Yamasaki, E., "Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test, Mutat. Res., 31, 347-364, 1975.

16. REPEATED DOSE TOXICITY

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8 Batch No. EN 29040, An. No. 4689
Method:	Although this study was not formally conducted under OECD guidelines, the method parallels the method described in OECD Guideline 409 "Subchronic Oral Toxicity – Non-Rodent: 90-Day study". In this study, a total of 48 Beagle dogs (6 males and 6 females/dose group) were given the test article in the diet for 13 weeks. After the administration period of three months, one animal per sex per dose group was fed the control diet for an additional 4 weeks. Clinical observations and food consumption were made daily. Body weight and auditory perception were measured weekly. Haematology, blood chemistry and urinalysis were carried out on weeks –1, 4, 9 and 13, and on week 17 for recovery animals. Eye examinations were performed pre-test and at weeks 13 and 17.
Species/strain:	Beagle Dogs
Age at initiation:	24 – 31 weeks
Sex:	Male/Female
No. animals/group:	6/sex
Route of administration:	Dietary
Exposure period:	13 weeks
Frequency of treatment:	Daily
Post exposure observation period:	4 weeks
Dose:	1000, 3000 and 10000 ppm
Control group:	Concurrent (diet without admixing the test article)
GLP:	Yes
Year:	1981

Results:	**NOEL:** 10000 ppm There were no adverse effects that could be related to treatment. No clinical symptoms and no signs of systemic toxicity were observed. Ophthalmic inspection revealed no changes related to treatment. No impairment of auditory perception was found. No animals died during the study. Food consumption, body weight gain and mean food conversion were unaffected by treatment. The results of the haematology, blood chemistry and urine analysis were unremarkable. An increase in total bilirubin concentration was observed at weeks 4 and 9, but not at week 13. As no other bilirubin linked parameter was changed, this observation was considered to be incidental and of no toxicological significance. Neither macroscopic nor microscopic changes that could be related to treatment were found. Organ weights and ratios for the compound treated dogs were comparable to those in the control animals.
Remarks:	This study is assigned a reliability code of 1 (reliable without restriction) according to the guidelines described by Klimisch *et al* (1997).
Reference:	"Final Report: TK 10042, 3-Month Toxicity Study on Dogs (Project No. 790539)", Ciba Geigy Limited, Basel, Switzerland. Dr. med R. Hess, 08/25/81.

17. REPRODUCTIVE TOXICITY

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8
Method:	Although not formally conducted under OECD guidelines, the methods in this study parallel OECD Guideline 416 "Two-Generation Reproduction Toxicity Study". Diets containing 0 (control), 1000, 3000, or 10000 ppm of the test material were fed continuously to both sexes throughout two generations. Animals of the F0 generation were maintained on their treatments for 10 weeks prior to mating. One male and one female were paired for mating for a period of 20 days. Dams were allowed to rear their young to Day 21 postpartum; 24 male and 24 female pups were retained as the F1 generation. Following selection of the F1 generation, a male and a female from each litter were selected for organ weight analysis and preservation of tissues. The remaining animals were sacrificed and examined macroscopically and discarded. F0 females that failed to produce a litter at the first mating were re-mated for a second 20-day period. Resultant litters were sacrificed on Day 8 postpartum. With the exception of the occasional animals that were involved in the remate, F0 parents were sacrificed following weaning of the F1 litters. Organ weight analysis and preservation of tissues was performed on all F0 parents. Animals of the F1 generation were kept on their respective diets weaning for 12 weeks prior to mating, which was carried out as described above. Dams were allowed to rear the pups until Day 21 post partum. Analysis of the F2 generation and F1 parents was carried out as described above. Throughout the study animals were observed for any clinical signs of toxicity. Food consumption, water intake and body weight gain was also monitored throughout the study.
Type:	Two-generation study
Species/strain:	CrL:COBS CD (SD) BR Rats
Sex:	Male/Female
Route of Administration:	Oral
Exposure period:	2 generations, 10 months
Frequency of treatment:	Daily dietary exposure

Premating exposure period:	Male: 10 weeks; Female: 10 weeks
Duration of the test:	2 generations, 10 months
Doses:	1000, 3000 and 10000 ppm
Control group:	Concurrent no treatment (standard diet)
GLP:	Yes
Year:	1984
Results:	NOEL Parental: 10000 ppm NOEL F1 Offspring: 10000 ppm NOEL F2 Offspring: 10000 ppm

General Parental Toxicity: No deaths occurred among animals of either the F0 or F1 generation nor were there any consistent effects which could be attributed to treatment, including any clinical signs of toxicity, food consumption, body weight gain and efficiency of food utilization, reproductive capacity as assessed by mating performance, pregnancy rate and duration of gestation, findings at terminal autopsy.
Toxicity to offspring: There were no adverse effects on litters of treated parents in either generation, as assessed by: (1) the incidence of total litter loss; (2) mean values of litter size, pup mortality, sex ratio, litter and mean pup weights; (3) findings at terminal necropsy. A suggestion of slightly faster growth rate was apparent among offspring at 10000 ppm in both generations, an observation which appeared to be independent of litter size and was endorsed by the noticeably higher mean litter weight in this group at termination.

The findings of this study indicated that, under the conditions of the test procedure, animals administered the test compound showed no substantial differences from their control counterparts and that their reproductive capacity was not impaired.

Remarks:	This study is assigned a reliability code of 1 (reliable without restrictions). This study was conducted under GLP guidelines. The report contains all of the information necessary to evaluate the adequacy and results.
Reference:	"Effects of TK 10042 on Reproductive Functions on Two Generations of the Rats", Huntingdon Research Centre, Huntingdon, Cambridgeshire, England. Audry M. Bottomley, 09/05/84.

18. DEVELOPMENTAL TOXICITY/ TERATOGENICITY

Two studies were conducted to assess the teratogenic potential. Both studies are given equal weight, and taken together are adequate to meet the necessary requirements for this endpoint.

A

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8
Method:	Female rats were mated overnight with males of proven fertility in a ratio of one male to three females. The day on which spermatozoa were found in the vaginal smear was designated as Day 0 of pregnancy. Throughout the experiment, successfully mated females were housed in groups of 5 in an air-conditioned room at a temperature of 22 °C ± 5 °C and a humidity of 56% ± 5%. The room was illuminated for 12 hours daily. Animals were provided ad libitum access to a standard diet and tap water. The compound was administered by oral gavage on Days 6 through 15 of pregnancy. During the treatment, general condition, weight gain, food consumption and symptomology were checked daily. Dams were autopsied and fetuses were removed by Caesarean section on Day 21 of pregnancy. The examinations were carried out in accordance with the World Health Organization (WHO) recommendations (WHO, 1967) and the technique described by Wilson, 1965.
Species/strain:	Sprague-Dawley Rats
Sex:	Female
Route of administration:	Oral gavage
Duration of the test:	10 Days
Exposure period:	Days 6 through 15 of gestation
Frequency of treatment:	Daily
Doses:	150, 500 and 1000 mg/kg in 1 mL/100 g bw
Control group:	Yes Concurrent
GLP:	No
Year:	1975

Results:

NOEL maternal toxicity: 1000 mg/kg
NOEL teratogenicity : 1000 mg/kg

Maternal general toxicity: At the low and intermediate dose levels, an increase in food consumption was noted during the treatment period. However, there was no effect on body weight gain.
Pregnancy/litter data: The rates of implantation and resorptions, as well as the average weights of the fetuses were comparable for all groups.
Foetal data: Embryonic development was not adversely affected by treatment. In both the low and intermediate dose group phalangeal nuclei of the hind limb and calcanei displayed higher rates of ossification than in the controls. This effect on the physiological growth may be associated with the above mentioned increase in food consumption by the dams. It was not observed in the high-dose group.

Remarks:

This study is assigned a reliability code of 2 (reliable with restrictions) based on the criteria described by Klimisch *et al* (1997). This study was not conducted under formal guidelines but the methods are standard.

References:

"Reproductive Study – TK 10042, Rat, Segment II (Test for Teratogenic or Embryotoxic Effects)", Ciba Geigy Limited, Basel, Switzerland, Dr. H. Fritz, 06/19/75.

World Health Organization Technical Report Service 364, 1967

Wilson, J.G., in: Teratology, Principles and Techniques; J.G. Wilson and J. Warkany eds., The University of Chicago Press, Chicago, 1965, pp. 262-277.

B

Test substance:	Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane CAS No. 6683-19-8
Method:	Female mice were mated overnight with males of proven fertility in a ratio of one male to four females. The day on which the sperm plug was found was designated as Day 0 of pregnancy. Throughout the experiment, successfully mated females were housed in groups of 5 in an air-conditioned room at a temperature of 22 °C ± 5 °C and a humidity of 56% ± 5%. The room was illuminated for 12 hours daily. Animals were provided ad libitum access to a standard diet and tap water. The compound was administered by oral gavage on Days 6 through 15 of pregnancy. During the treatment general condition, weight gain, food consumption and symptomology were checked daily. Dams were autopsied and fetuses were removed by Caesarean section on Day 18 of pregnancy. The examinations were carried out in accordance with the World Health Organization (WHO) recommendations (WHO, 1975) and the technique described by Wilson, 1965.
Species/strain:	NMRI derived Albino Mice
Sex:	Female
Route of Administration:	Oral gavage
Duration of the test:	10 Days
Exposure period:	Days 6 through 15 of gestation
Frequency of treatment:	Daily
Doses:	150, 500 and 1000 mg/kg in 0.1 mL/10 g bw
Control group:	Yes Concurrent vehicle (2% aqueous carboxymethyl cellulose)
GLP:	No
Year:	1975
Results:	**NOEL maternal toxicity:** 1000 mg/kg **NOEL teratogenicity:** 1000 mg/kg

Maternal general toxicity: No reactions to treatment were noted. Body weight gain and food consumption were comparable for all groups.

Pregnancy/litter data: The rates of implantation and resorptions, as well as the average weights of the fetuses were comparable for all groups.

Foetal data: Skeletal assessment revealed minor deviations from controls in the low and high dose groups. At the 150 mg/kg dose level, the incidences of ossification of the phalangeal nuclei of the hind limb and calcanei were significantly higher than controls. An increase in the number of still incompletely ossified sternebrae was observed at the high dose. Although a higher rate of ossification of the phalangeal nuclei of the hind limb and calcanei in the fetuses was observed, there was no consistent dose-response effect. A slight increase in the number of still incompletely ossified sternebrae was observed at the 1000 mg/kg dose. The compound is considered to be nonteratogenic in the mouse

Remarks:

This study is assigned a reliability code of 2 (reliable with restrictions) based on the criteria described by Klimisch *et al* (1997). This study was not conducted under formal guidelines but the methods are standard.

References:

"Reproductive Study – TK 10042, Mouse, Segment II (Test for Teratogenic or Embryotoxic Effects)", Ciba Geigy Limited, Basel, Switzerland, Dr. H. Fritz, 08/28/75.

World Health Organization Technical Report Service 563, 1975.

Wilson, J.G., in: Teratology, Principles and Techniques; J.G. Wilson and J. Warkany eds., The University of Chicago Press, Chicago, 1965, pp. 262-277.

GENERAL REFERENCE

Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25:1-5, 1997.

Definition of codes

1 = Valid without restriction
1a: GLP guideline study
1b: Comparable to guideline study
1c: Meets national standard methods (AFNOR/DIN)
1d: Meets generally accepted scientific standards and is described in sufficient detail

2 = Valid with restriction
2a: Guideline study without detailed documentation
2b: Guideline study with acceptable restrictions
2c: Comparable to guideline study with acceptable restrictions
2d: Meets national standard methods with acceptable restrictions
2e: Meets generally accepted scientific standards, well documented and acceptable for assessment
2f: Accepted calculation method
2g: Data from Handbook or collection of data

3 = Invalid
3a: Documentation insufficient for assessment
3b: Significant methodological deficiencies
3c: Unsuitable test system

4 = Not assignable
4a: Abstract
4b: Secondary literature
4c: Original reference not yet available
4d: Original reference in foreign language
4e: Documentation in sufficient for assessment